UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,053	10/19/2001	Apollon Papadimitriou	CIBT-P01-097	4732

28120 7590 08/21/2003

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	9

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/890,053	PAPADIMITRIOU ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-10* ~~are~~ subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-10 are pending in the instant application.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-8 and 10, drawn to pharmaceutical compositions comprising a hydrophobically modified hedgehog protein and a biodegradable protein as a carrier and process of making the same.

Group II, claim(s) 9, drawn to a method of administration of hydrophobically modified hedgehog protein.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: hydrophobically modified hedgehog proteins are well known in the art and therefore cannot constitute a unifying technical feature.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species of additional component of the composition are as follows:

hyaluronic acid and alginate.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify

the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The claims are deemed to correspond to the species listed above in the following manner:

Hyaluronic acid, claim 4
Alginate, claim 4

The following claim(s) are generic: 1-3 and 5-10.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: they are structurally and functionally distinct chemical compounds and therefore cannot constitute a unifying technical feature.

During a telephone conversation with David Halstead on June 20, 2003 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-8 and 10, and species of hyaluronic acid. Affirmation of this election must be made by applicant in replying to this Office action. Claim 9 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

3. The disclosure is objected to because of the following informalities: there is a blank section in the middle of page 6, which has disconnected sentences.

Appropriate correction is required.

Claim Objections

4.1 Claims 4-7 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. Multiple dependent claims must refer to the claims from which they depend in the alternative only, not inclusively. See M.P.E.P. 608.01(n) for acceptable multiple dependent claim wording.

4.2 Claim 5-7 are also objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only, and cannot depend from any other multiple dependent claim. For unacceptable multiple dependent claim wording, see MPEP § 608.01(n) *B.* 4., for an example showing reference back to another multiple dependent claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5.1 Claims 1-8 and 10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,207,718. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed to pharmaceutical compositions comprising hedgehog proteins. The scope of the patented and instant claims differs in the combinations of carriers and additives recited, However, the patented claims recite carriers and additives that are also recited in the instant claims. Also, while the patented claims do not recite a hydrophobically modified hedgehog protein, it is noted that naturally occurring hedgehog proteins are hydrophobically modified. Thus, the patented claims embrace compositions comprising hydrophobically modified hedgehog proteins.

5.2 Claims 1-8 and 10 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,207,718. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which

corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2). The claims are rejected for the reasons given above.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 4-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 is indefinite because it is not clear if the hyaluronic acid or alginate is the carrier, or if they are in addition to the carrier. If it is intended that they are in addition to the carrier, it is suggested that the word "further" be inserted before the word "containing" to clarify the claim. Claims 5-7 are indefinite from depending on claim 4.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pepinsky et al., U.S. Patent No. 6,444,793, filed 12/3/97, (provisionals filed 9/10/98, 6/17/98, 3/20/98 and 12/3/97) in view of Easton et al., U.S. Patent No. 4,614,794, issued Sept. 30, 1986, and further in view of Usala et al., U.S. Patent No. 6,231,881, filing date July 10, 1998.

Claims 1-6 and 8 encompass pharmaceutical compositions containing hydrophobically modified hedgehog protein and a biodegradable protein as carrier, wherein the carrier may be soluble or insoluble cross-linked collagen, wherein the composition may also contain hyaluronic acid or alginate, and wherein the hedgehog protein is at a concentration of 0.1-100 mg/ml, wherein the composition is buffered in a range between 4.5 and 10, process for the production of

a pharmaceutical composition wherein a hydrophobically modified hedgehog protein in combined in a therapeutically effective amount with a biodegradable protein as carrier.

Pepinsky et al. discloses hydrophobically modified hedgehog proteins which are naturally occurring (column 2, lines 46-54) or chemically modified with various hydrophobic moieties (claims 11, 15, 17-20, for example), and that appending a hydrophobic moiety can enhance the proteins's activity (column 7, lines 51-67), pharmaceutical compositions comprising the hydrophobically modified hedgehog proteins (column 8, lines 32-35, column 39, lines 28-36), and teach advantages of administering the modified proteins (column 38, line 42 to column 40, line 17, column 40, line 54 to column 41, line 25). Although Pepinsky et al. do not specifically state that the pharmaceutical composition be buffered in a range between pH 4.5 and 10 and that the pharmaceutical composition contain hedgehog protein at a concentration of 0.1-100mg/ml, Pepinsky et al. provide ample guidance on how to determine optimal pharmaceutical compositions, and that one of ordinary skill in the art would know how to make such determinations. Pepinsky et al. state, starting at column 39, line 28:

> For therapeutic use, hydrophobically-modified proteins of the invention are placed into pharmaceutically acceptable, sterile, isotonic formulations and optionally are administered by standard means well known in the field. The formulation is preferably liquid or may be lyophilized powder. It is envisioned that a therapeutic administration of, for instance, a multimeric protein complex may comprise liposomes incorporating the derivatized proteins described herein.
>
> It will be appreciated by persons having ordinary skill in the art that the particular administration, dosage, and clinical applications of a hydrophobically-modified protein of the invention will vary depending upon the particular protein and its biological activity.

Starting at column 40, line 54, Pepinsky et al. state:

The protein compositions to be used in therapy will be formulated and dosages established in a fashion consistent with good medical practice taking into account the disorder to be treated, the condition of the individual patient, the site of delivery of the isolated polypeptide, the method of administration, and other factors known to practitioners. The therapeutic may be prepared for administration by mixing a protein, a protein-containing vesicle, or a derivatized complex at the desired degree of purity with physiologically acceptable carriers (i.e. carriers which are nontoxic to recipients at the dosages and concentrations employed).

It is envisioned that local delivery to the site will be the primary route for therapeutic administration of the proteins of this invention. Intravenous delivery, or delivery through catheter or other surgical tubing may also be envisioned. Alternative routes include tablets and the like, commercially available nebulizers for liquid formulations, and inhalation of lyophilized or aerosolized formulations. Liquid formulations may be utilized after reconstitution from powder formulations.

The dose administered will be dependent upon the properties of the vesicle and protein employed, e.g. its binding activity and in vivo plasma half-life, the concentration of the vesicle and protein in the formulation, the administration route, the site and rate of dosage, the clinical tolerance of the patient involved, the pathological condition afflicting the patient and the like, as is well known within the skill of the physician. Generally, doses of from about 5.times.10.sup.-7 to 5.times.10.sup.-9 Molar of protein per patient per administration are preferred, although the dosage will depend on the nature of the protein. Different dosages may be utilized during a series of sequential administrations.

The invention is also directed towards a pharmaceutical formulation which includes a hedgehog protein modified according to the invention in combination with a pharmaceutically acceptable carrier. In one embodiment, the formulation also includes vesicles.

Pepinsky et al. do not teach that the pharmaceutically composition contain a biodegradable protein such as collagen, as carrier, or additionally contain a hyaluronic acid or alginate.

Easton et al. teach pharmaceutical compositions or complexes that contain soluble collagen (Example 2 and 4), insoluble collagen (Example 1 and 5), and that also may contain

hyaluronic acid (column 1, lines 3-10), or alginate (abstract, column 2, lines 63-68, claims 1-14). Easton et al. also teach that such complexes may be used in surgical implants (column 1, lines 38-46), and that a cross-linked complex may be used to form a relatively non-biosorbable wound dressing, whereas a non-crosslinked complex may be used to form a biosorbable dressing (column 3, lines 33-46), and that the composition of the complex and methods of preparation can be varied and will result in complexes having different stabilities, pore sizes and uses (column 3, line 47 to column 4, line 28).

Usala et al. teach that an important feature of the matrix of the present invention is the increased level of polar amino acid groups such as arginine (abstract, column 9, lines 57-61). The addition of polar amino acids increases the number of hydrogen bonding moieties which subsequently increase the rigidity of the matrix.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to make a pharmaceutical composition comprising a hydrophobically modified hedgehog protein, as taught by Pepinsky et al., but using a collagen or collagen/alginate matrix of Easton et al., and additionally adding a polar amino acid such as arginine, as taught by Usala et al. Since Pepinsky et al. teaches that as the half-life of hedgehog is very short after systemic application and that multiple injections are required to achieve a robust response to the protein, the higher potency of the modified form and the possibility of formulation in liposomes provides a means of achieving a response with fewer treatments, and that the more limited the range over which a protein diffuses away from the site of administration, the higher the local concentration (column 38, line 62 to column 39, line 1, column 39, lines 13-15), and that it is envisioned that local delivery to the site will be the

primary route for therapeutic administration (column 40, lines 65-67). Since Easton et al. teaches that pharmaceutical complexes comprising collagen and alginate can be made that have varying degrees of biodegradability and pore size, and since Usala et al. teach that addition of arginine can increase the rigidity of the matrix, one of ordinary skill in the art would be motivated to make and use such complexes for local administration of hydrophobically modified hedgehog proteins, which could be made to allow diffusion of the protein at different rates and that had various stabilities. There would be a reasonable expectation of success, since making and using such collagen/therapeutic protein complexes were successfully used in methods of treatment.

8. The USPTO is participating in a search exchange pilot program with the European Patent Office (EPO). As part of the pilot program, the USPTO has received a copy of the Search Report prepared by the EPO on the counterpart EP application for which priority under 35 U.S.C. 119(a) is claimed. The references cited in the EPO Search Report were submitted in the IDS filed June 30, 2002 and have been considered by the examiner.

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elyabeth C. Kemmerer

Eileen B. O'Hara, Ph.D.

ELIZABETH KEMMERER
PRIMARY EXAMINER

Patent Examiner